REVIEW ARTICLE

Novel Drugs for Cessation of Smoking

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INTRODUCTION

Each year, 8 million premature deaths are caused by tobacco use worldwide[1]. Quitting smoking can lower these health risks and lengthen life expectancy, but more than 95% of unassisted attempts to stop smoking fail within six months due to tobacco's high level of addiction[2]. Nicotine interacts with nicotinic acetylcholine receptors (nAChRs) in the central nervous system to cause addiction. Several attempts to stop smoking are frequently necessary to achieve long-term tobacco abstinence, according to a significant body of evidence[3, 4].

Novel drugs for smoking cessation

1) Cytisinicline

It is a plant-based single enantiomer alkaloid whose molecular structure resembles nicotine, and cytisinicline and nicotine. It functions as a partial agonist, blocking nicotine from attaching to nicotinic acetylcholine receptors and causing the release of dopamine in mesolimbic loci, such as the amygdala[5-7].

Mechanism of action of Cytisinicline as a partial nAChR agonist in treating nicotine addiction is by two ways: 1) Some release of dopamine are maintained by its partial agonism effect (although lower than the level stimulated by nicotine) and therefore it reduces craving and other withdrawal symptoms 2) At the same time its partial antagonism effect reduces its nicotine binding, therefore reducing pleasure and other rewarding effects of smoking.

Cytisinicline has been approved and used as a smoking cessation medication in Europe since the 1980s, [8, 9] with an administration schedule consisting of 1.5-mg tablets in a downward titration, from 6 tablets/day to 1 tablet/day over a 25-day period.

810 adult smokers participated in the placebo-controlled ORCA-2 research (NCT04576949), which assessed the safety and effectiveness of cytisinicline for smoking cessation. Patients with an average age of 54 years were randomly assigned (1:1:1) to receive either placebo, or cytisinicline 3mg administered three times per day for either six or twelve weeks. Following the randomization, they were observed for 24 weeks to see if they had stopped smoking, and behavioural assistance was given throughout the trial[10].

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors are used to treat cognitive impairments brought on by Alzheimer's disease[11]. They are reportedly successful at battling drug addiction, according to recent reports (including nicotine dependence). Acetylcholinesterase inhibitors, such as donepezil and galantamine, can decrease the amount of nicotine that rats self-administer[12,13]. Compared to the control group, the rivastigmine group significantly reduced daily cigarette smoking (30%), carbon monoxide exhaled (32%), and tobacco craving (18%) during the course of a 12-week, randomised, placebo-controlled experiment[14].

Agents affecting GABA receptors

GABA is a non-protein amino acid. It is a crucial neurotransmission inhibitor in the human brain. Through the allosteric regulation of a non-benzodiazepine site on the GABA-A receptor, topiramate promotes GABAergic neurotransmission. In a randomised, 10-week study, the prevalence of 4-week continuous abstinence was found to be 5% in the placebo group, 26% in the topiramate group, and 37% in the topiramate plus nicotine patch group. A difference between the topiramate plus nicotine patch and placebo groups was seen in 88 pairwise comparisons ($p = 0.042$), but not between the topiramate and placebo groups ($p = 0.18$)[15].

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N-Acetyl Cysteine (NAC)

NAC is a well-known, well-tolerated, and reasonably priced nutraceutical supplement that modifies immune-inflammatory, glutamatergic, neurotrophic, oxidative, and neurotrophic pathways while raising intracellular glutathione levels, an important antioxidant[16]. In a study conducted by Prado and colleagues, NAC treatment significantly decreased the number of cigarettes smoked each day as well as the amount of carbon monoxide inhaled (mean SD = 10.4 8.6 ppm in the NAC-treated group versus 1.5 4.5 ppm in the placebo group; mean SD = 10.9 7.9 in the NAC-treated group)[17].

Cytisine

Cytisine is a plant-based medication. In central and eastern Europe, it has been used for smoking cessation for more than 50 years. A two-arm, parallel-group, randomised, non-inferiority trial is now being conducted to examine the effectiveness, safety, and cost-effectiveness of cytisine with varenicline in the treatment of tobacco dependence.

Other agents

Table 1: Clinical trials for other agents are summarized.

Trial Drug/Phase	Author	Mechanism of action	Result of trial
Exenatide Phase I/II	Yammine	GLP-1 agonist	Recruiting
Guanfacine Phase II	MckeeSA	Alpha-2-adrenergic agonist	Active, not recruiting
Lorcaserin Phase II	Anderson D	Selective 5-HT (2C)agonist	Lorcaserin (10 mg, b.i.d.), 15.31%; Lorcaserin (10 mg, q.d.), 8.72%; placebo, 5.64%
Nadolol Phase II	Castro M	Nonselective beta-blocker	Nadolol, 61.6%; placebo, 50%
D-cycloserine Phase I/ II	Hill KP	Partial NMDA-agonist	D-cycloserine, 2.57 ± 3.63 cigarettes/day; placebo, 0.29 ± 0.25 cigarettes/day.
AZD8529 Phase II	Gyaw S	Positive allosteric modulator at the mGluR2 receptor	AZD8529 (low dose), 9.6%; AZD8529 (high dose), 10.0%.
GSK598809 Phase II	Fava M	D3 antagonist	GSK598809, 0%; placebo, 0%
Liraglutide Phase II	Ashare RL	Long-acting analogue of human GLP	Recruiting
AXS-05 Phase II	Davis JM	5-HT2A receptor antagonist	Active, Not recruiting
Doxazosin Phase II	Mckee SA	Selective antagonist at postsynaptic α1-adrenergic receptors.	Doxazosin (8 mg), 27.557 ± 6.409 (stress) and 23.776 ± 7.192 (neutral); doxazosin (4 mg) 32.128 ± 7.494 (stress) and 26.790 ± 8.410 (neutral); placebo, 11.304 ± 7.407 (stress) and 23.474 ± 8.312 (neutral)

CONCLUSION

It is undeniable that smoking is unhealthy. There is enough proof to conclude that smoking causes malignancies of the mouth, pharynx, larynx, lungs, and other organs. It is ideal for all healthcare professionals to be aware of every patient's smoking status and to offer every smoker suitable, comprehensive guidance on quitting. The use of NRT will be very beneficial for patients who want to stop smoking.

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